IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/519,342	Confirmation No. 2504
Applicant	:	Li et al.	
Title	:	METHODS AND COMPOSITIONS FOR MANIPULATING THE GUIDED NAVIGATION OF ENDOTHELIAL TUBES DURING ANGIOGENESIS	
Filed	:	September 21, 2005	
TC/A.U.	:	1647	
Examiner	:	David S. Romeo	
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Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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DECLARATION

37 C.F.R. § 1.132 DECLARATION OF DR. DEAN YAW LI

TO THE COMMISSIONER FOR PATENTS:

I, Dean Y. Li, declare as follows:

1. I am an inventor named in the above-identified patent application.

2. I reside at 1416 South Wasatch Drive, Salt Lake City, Utah 84108.

3. In 1983, the University of Chicago in Chicago, Illinois, awarded me a Bachelor of Arts degree in Chemistry. In 1990, Washington University in St. Louis, Missouri, awarded me an M.D. in medicine and a Ph.D. in biochemistry.

4. Since 1990, I have held various academic positions. From 1990 – 1992, I was an Internal Medicine Intern and an Internal Medicine Resident at Barnes Hospital at Washington University Medical Center. From 1992 – 1994, I completed a clinical

fellowship in Cardiology at Barnes Hospital at Washington University Medical Center. From 1994 – 1995, I was a Research Associate at the Eccles Institute of Genetics at the University of Utah. From 1995 – 1998, I was an Instructor in the Division of Cardiology at the University of Utah Medical Center. From 1998 – 2002, I was an Assistant Professor in the Division of Cardiology and the Progarm in Human Molecular Biology & Genetics at the University of Utah Medical Center. From 2003 – 2006, I was an Associate Professor of Medicine at the University of Utah Medical Center. In 2007, I was named Professor of Medicine, H.A. and Edna Benning Endowed Chair, at the University of Utah Medical Center, and from 2004 – present, I have been an Associate Director of the M.D./Ph.D. program at the University of Utah Medical Center.

5. I am a co-founder of Hydra Biosciences, Cambridge, Massachusetts, and from 2001 – 2003, I served as Head of Research and Development for Hydra Biosciences. From 2004 – present, I have served on a Scientific Advisory Board for Hydra Biosciences.

6. I am a co-founder of Navigen Pharmaceuticals, Inc. From 2006 – present, I have served as the Chief Scientific Officer of Navigen Pharmaceuticals, Inc. Navigen Pharmaceuticals, Inc. has rights to the above-identified patent application through a license from the University of Utah Research Foundation.

7. From 1983 – 1990, I participated in the NIH Medical Scientist Training Program. In 1988, I received the Olin Award for Excellence in Biomedical Research at Washington University in St. Louis, Missouri. From 1994 – 1997, I was a recipient of the Howard Hughes Physician Scientist Postdoctoral Fellowship Award. In 2006, I received the Established Investigator Award from the American Heart Association and the Clinical Scientist Award in Translational Medicine from the Burroughs Wellcome Foundation.

8. I have authored many of scientific articles, primarily in the disciplines of biochemistry and molecular and cellular biology as applied to the formation, function and health of vascular systems. For reference, I have attached a listing of exemplary scientific articles as Appendix A to this Declaration.

9. Claims 7 through 9 and 22 (as amended by an Amendment and Response to Office Action, filed herewith) are directed to methods of preventing guided navigation of endothelial tubes during angiogenesis to a target cell mass, wherein said endothelial tubes express a Robo-4 receptor. The method of claim 7 involves activating said Robo-4 receptor, wherein activating said Robo-4 receptor disrupts the guided navigation of the endothelial tubes toward the target cell mass. The method of claim 8 involves providing a ligand capable of activating said Robo-4 receptor and exposing said endothelial tubes to the ligand, wherein said exposure of said endothelial tubes to said ligand inhibits the guided navigation of the endothelial tubes toward the target cell. The method of claim 9 specifies that providing a ligand capable of activating said Robo-4 receptor comprises providing a Slit ligand. The method of claim 22 further specifies that providing a ligand capable of activating said Robo-4 receptor comprises providing a human Slit2, or a fragment thereof.

10. Claims 19 through 22 (as amended by an Amendment and Response to Office Action, filed herewith) are directed to methods of preventing angiogenesis in endothelium tissue expressing Robo-4 receptor, the methods comprising activating said Robo-4 receptor, wherein activating said Robo-4 receptor inhibits migration of endothelial cells. The method of claim 20 specifies that activating said Robo-4 receptor comprises providing a ligand capable of activating said Robo-4 receptor and exposing the endothelium tissue to the ligand, wherein said exposure of said endothelium tissue to said ligand inhibits migration of endothelial cells. The method of claim 21 specifies that providing a ligand capable of activating said Robo-4 receptor comprises providing a Slit ligand, and the method of claim 22 further specifies that providing a ligand capable of activating said Robo-4 receptor comprises providing a human Slit2, or a fragment thereof.

11. In the April 29, 2008 Office Action, claims 7 through 9 and 19 through 22 are rejected under 35 U.S.C. § 112, first paragraph. As support of this rejection, references that 1) assertedly contravene the subject matter recited in the rejected claims, 2) establish the art as unpredictable, or 3) support a conclusion that vascular

guidance is complex are cited in the Office Action. I have reviewed this rejection and each reference cited in support thereof.

12. Suchting (FASEB J. 2005 Jan; 19(10: 121-3) does not contravene the subject matter recited in the rejected claims. It is noted in the Office Action that Suchting reports that soluble Robo-4 receptor inhibits in-vivo angiogenesis and endothelial cell migration, and the Office Action argues "Suchting was unable to demonstrate interaction between any known Slit protein and Robo-4 . . . ." (See, Office Action, p. 4, lines 12-18 and p. 8, lines 21-22). However, the experiments described in Suchting utilized an isolated, soluble receptor ectodomain in a BIAcore binding assay, an artificial and in vitro system. Suchting does not utilize a full-length, membrane bound Robo-4 receptor in the context of whole cells, endothelial tubes or in-tact tissue, and in that manner, Suchting is distinguishable from the subject matter recited in the rejected claims. Suchting's experiments do not reflect the behavior of Robo-4 or its response to Slit proteins in whole cells, endothelial tubes or in-tact tissues expressing Robo-4.

13. Zhu (Neuron. 1999 Jul; 23(3): 473-485) does not contravene the subject matter recited in the rejected claims. In particular, it is asserted in the Office Action that, in the work reported in this publication, using "the aorta ring assay to investigate whether Slit repels endothelial cells . . . ," "[i]t was found that Slit did not repel or attract cells migrating out of the aorta . . . ." (See, Office Action, p.6, lines 18-20). However, the authors of Zhu did not use isolated, partially purified or purified Slit protein in their experiments. Instead, HEK cells expressing Slit protein were used. It is known that mesenchymal cells, such as HEK cells, secrete a number of factors and cytokines, many of which are proangiogenic. Therefore, the experimental results provided in Zhu are not predictive of effects of exposing endothelial cells, endothelial tubes, or in-tact tissue expressing Robo-4 to an isolated ligand, such as a Slit protein, capable of activating the Robo-4 receptor.

14. Kaur (J Biol Chem. 2006 April 21; 281(16): 11347-56), Bedell (Proc Natl Acad Sci USA. 2005 May 3; 102(18):6373-8) and Eichmann (Genes Dev. 2005 May 1; 19(9): 1013-21) do not contravene the subject matter recited rejected claims. Eichmann is a review publication that does not take into account the information provided in the

as-filed specification of the above-referenced application. With respect to Kaur and Bedell, both references focus on the role of zebrafish Robo-4 in the vascular development of zebrafish, and neither reference addresses ligands capable of activating Robo-4.

15. Migration of endothelial cells and formation and migration of endothelial tubes are essential in the process of angiogenesis. As is supported by the experimental evidence provided in the specification of the above-identified patent application, activation of Robo-4 expressed in endothelial cells inhibits migration of such endothelial cells and provides a negative cue to the formation and migration of endothelial tubes. (See, e.g., the experimental results described in ¶43 through ¶45 and in FIG. 6 and FIG. 7). The specification of the above-identified patent application further reveals the association of Robo-4 expressed in the context of a cell surface and Slit protein (See, e.g., the experimental results described in ¶39 and ¶40 and in FIG. 5), and evidences that the presence of expressed Robo-4 is sufficient to render cells responsive to Slit protein (See, e.g., the experimental results described in ¶43 through ¶44 and in FIG. 6). In addition, the specification of the above-identified application provides specific descriptions of Robo-4 receptor, Slit proteins and methods that would allow one of ordinary skill in the art to confirm the results described therein and carry out the subject matter recited in the rejected claims.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/29/08

Dean Y. Li

APPENDIX A

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